REMARKS

Claims 1-15 are being examined in this application. These claims stand rejected, under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 102. Claims 1-15 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting, and claim 15 is objected to for form. Each of these issues is addressed below in the order in which it appears in the Office action.

Amendments

Claims 1, 4-6, 8, 9, 14, and 15 have been amended, and new claims 43-53 have been added. The amendment to claim 1 finds support in claim 2, which is now canceled, and in the specification, for example, at page 3, lines 9-10; page 14, lines 29-30; page 16, lines 12-13; page 24, line 20; pages 36-39; page 46, lines 4-6; pages 49-51; and pages 55-58.

The amendments to claims 4-6, 8, 9, 14, and 15 conform their language to that of amended claim 1 or correct spelling errors; additionally, the amendment to claim 6 finds support in the specification, for example, at 48, line 31 – page 49, line 1, and the amendment to claim 9 finds support in the specification, for example, at page 7, lines 30-31.

New claims 43-53 also find support in the specification, for example, as follows: claim 43, page 36, line 23; claims 44-46, pages 49-51 and 55; claim 47, page 46, lines 25-26 and page 51, lines 5-12; claim 48, pages 49-51 and 55; claim 49, page 46, line 26 and page 55, line 25; claim 50, pages 49-51 and 55; claim 51, page 51, line 20; claim 52, page 42, line 22 – page 43, line 5; and claim 53, page 51, lines 26-28.

Applicants reserve the right to pursue all canceled subject matter in this or a future, related application.

Claim Objection

Claim 15 stands objected to as being of improper form based on the assertion that the claim fails to further limit base claim 1. The Office asserts that claim 15 "appears to only set forth a description of what occurs after practicing the steps of claim 1." This objection is respectfully traversed.

Claim 15 requires that a recipient oocyte generated by the method of claim 1 express particular donor cell-specific proteins at levels that approach those of control oocytes. While it is true, and Applicants agree, that carrying out the steps of claim 1 can result in this outcome, the levels required by claim 15 are optimized results for particular donor cells and are not required by claim 1. Thus, claim 15 represents a preferred outcome for claim 1, making the claim narrower than claim 1 and in compliance with 37 C.F.R. § 1.75(c). This objection should be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-15 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite based on particular claim terms. These rejections are addressed as follows.

Claim 1 stands rejected, as being indefinite, for use of the term "permeabilized cell." The Office states that the definition of "permeabilization" includes the formation of pores in a plasma membrane or partial or complete removal of a plasma membrane, and that this definition is inconsistent with the use of the term "cell" in the claim. This basis for the rejection is respectfully traversed.

Applicants first note that the definition referred to by the Office is not for the term "permeabilized cell," but rather for "permeabilization," a general technique that can be carried out to varying degrees that range from small perforations in a plasma membrane to complete destruction of the membrane. Applicants do utilize permeabilization to generate their donor cells, but, for the purpose covered by the present claims, it is quite clear that the plasma membrane is not completely removed. This would be readily understood by

one of skill in the art, particularly in view of the present specification where Applicants set forth extensive teachings and examples of their permeabilized cell technology, all of which involve a degree of plasma membrane disruption that does not completely destroy the membrane and that allows for optional membrane resealing. The fact that the plasma membrane is not completely removed is further supported by both the use of the term "cell" in claim 1, a term that indicates that at least some portion of the membrane is intact, and by dependent claim 5 which requires resealing of the permeabilized cell generated in claim 1. This dependent claim 5 makes logical sense only if a plasma membrane is present in some form to be resealed. For all of these reasons, Applicants submit that original claim 1 is definite.

Nonetheless, for clarification purposes, this claim has been amended to require that the permeabilized cell have "pores in its plasma membrane or partial, but not complete, removal of its plasma membrane." This basis for the indefiniteness rejection of claim 1 should be withdrawn.

The clarifying amendment to claim 1 and the above arguments apply with equal force to the rejection of claim 5. The Office contends that this claim is indefinite because it requires the resealing of the plama membrane, but base claim 1 "encompass[es] the complete removal of the membrane." As indicated above, the specification does not support this interpretation of the language of claim 1, and this basis for the rejection may also be withdrawn.

Claim 1 stands further rejected on the basis that it is unclear what factors are being removed or added during the incubating step and that it is also unclear "how agents can be both added or removed and still result in a cell that results in a fetus, in particular, because simply providing the fusion of a somatic cell to an oocyte under art recognized conditions can result in a viable fetus and offspring." Claims 1-15 also stand rejected on this same general basis, with the Office asserting that these claims lack essential elements because they do not define the conditions or agents that result in reprogramming of the

cell. As applied to the present claims, these bases for the rejection are respectfully traversed.

Claim 1 and its dependent claims now require that the permeabilized cell be incubated in a mitotic cell extract. As demonstrated by Applicants in the present specification, this incubation step facilitates reprogramming of the donor cell, presumably due to exchange of factors between the cell and the extract, and results in embryos having protein expression patterns that more closely resemble *in vitro* fertilized embryos than do cloned embryos produced with the sort of traditional cloning methods referred to by the Office. Furthermore, when carried out using permeabilized cells, the methods result in improved cloning efficiencies, as indicated by Table 3 of the present specification.

Thus, the present claims meet all of the Office's objections and satisfy the case law. The claims specify incubation in a mitotic cell extract -- the condition that in combination with insertion into the oocyte facilitates reprogramming of the donor cell. And this method is set forth using terms that are definite. There is no question that skilled practitioners in this area understand the term "mitotic cell extract," and Applicants have demonstrated the technique using this extract to be workable. Applicants need not specify exactly which factors are added from the extract or removed from the permeabilized cell; nowhere is such specificity required by the case law. Finally, while not relevant to § 112, second paragraph, in response to the Office's assertion, Applicants point out that, while "art recognized conditions can result in a viable fetus and offspring," the present methods provide a significant improvement on these conventional techniques with respect to cloning efficiencies.

The § 112, second paragraph rejections may be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-15 also stand rejected under 35 U.S.C. § 102(e) as being anticipated by Robl et al. (U.S. Patent Pub. No. 2004/0068760), Collas et al. (U.S. Patent Pub. No.

2002/0142397 A1), or Chapman (U.S. Patent Pub. No 2002/0001842 A1). Claims 1, 3, 7, and 9-15 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Machatay (U.S. Patent No. 6,211,429). And claims 1-15 stand further rejected under 35 U.S.C. § 102(f) based on the assertion that the list of inventors provided by Applicants is incorrect. These rejections are respectfully traversed.

Beginning with Robl (U.S. Patent Pub. No. 2004/0068760), Applicants point out that this reference does not anticipate any of claims 1-15 because the description of the present invention in the published Robl application is not prior art to the present claims. The only description of the present invention in Robl was added, for the first time, on May 19, 2003 (and is indicated in the Robl publication by a claim to priority to the present application). As this disclosure occurred after the present application's filing date of December 21, 2001, it does not constitute prior art under 35 U.S.C. § 102(e), and the rejection may be withdrawn.

Collas (U.S. Patent Pub. No. 2002/0142397) also does not anticipate the present claims. Present claim 1 and all dependent claims are directed to a "method of cloning a non-human mammal" and require the cloning-related steps of "inserting said permeabilized cell into a nucleated or enucleated oocyte" and "transferring said recipient oocyte or an embryo formed from said recipient oocyte into the uterus of a host mammal under conditions that allow said recipient oocyte or said embryo to develop into a fetus." None of these elements of the present claims are disclosed in Collas, which is a reference that involves the reprogramming of somatic cells into other somatic cells (for example, fibroblasts into T cells). Such cell fate reprogramming does not require insertion of a permeabilized cell into an oocyte, and in fact oocytes are nowhere mentioned in the Collas publication. Nor does the Collas cell fate technique involve formation of an embryo or transfer of that embryo into the uterus of a host animal. These are all steps required by the present claims that are completely absent from the Collas teaching. The rejection over Collas may be withdrawn.

With respect to Chapman (U.S. Patent Pub. No. 2002/0001842 A1), Applicants point out that claim 1 and all dependent claims cover a cloning technique that requires the use of a permeabilized cell "comprising pores in its plasma membrane or partial, but not complete, removal of its plasma membrane." Chapman, as correctly indicated by the Office, teaches methods purported to de-differentiate a cell through introduction of cytoplasm from a more primitive cell type. Chapman discusses cloning only briefly, and this discussion is limited to traditional forms of cloning, none of which involve methods that exploit permeabilized cells. Chapman therefore cannot anticipate the present claims.

The rejection of claims 1, 3, 7, and 9-15 over Machatay (U.S. Patent No. 6,211,429) should also be withdrawn. This rejection turns on the assertion that the "present claims broadly encompass providing an isolated nucleus to an oocyte, and using said resulting cell to produce a cloned fetus. As such, the present methods encompass nuclear transfer methodology." This assertion is incorrect. As indicated above, Applicants' claims require the use of permeabilized cells, which have disrupted (but existent) plasma membranes; these cells are not isolated nuclei, and the present methods therefore do not encompass nuclear transfer techniques. This rejection may be withdrawn.

Finally, with respect to the rejection of claims 1-15, under 35 U.S.C. § 102(f), Applicants submit that inventorship of the present claims is correct, and is not called into question by the inventors listed on the patent publication of either Robl et al. (2004/0068760) or Collas et al. (2002/0142397). The rejection is based on the Office's assertion that the "instantly claimed invention is set forth in the specification and is encompassed in practicing the methods set forth in Robl et al. (2004/0068760) and Collas et al. (2002/0142397). However, the inventive entity of each of the applications is different."

This rejection is traversed because the *inventions claimed* in each of these applications is different, and the inventive entities should, and do, therefore differ.

Present claims 1-15 are directed to methods for cloning a non-human mammal that combine initial incubation in a mitotic cell extract with a permeabilized cell transfer technique. As indicated, the inventors of this method are Robl, Collas, Sullivan, and Kasinathan.

In contrast, Robl et al. (2004/0068760) claims a number of techniques and compositions, including transgenic ungulates and transgenic ungulate somatic cells encoding xenogenous immunoglobulins, transgenic ungulates and transgenic ungulate somatic cells having mutations in endogenous antibody genes, hybridomas formed from such claimed cells, methods of producing antibodies that involve the use of such ungulates, and a series of methods for producing such ungulates using cloning techniques that include, among others, the permeabilized cell technique. This Robl application lists, as inventors, Robl, Collas, Sullivan, Kasinathan, Goldsby, Kuroiwa, Tomizuka, and Ishida. Four of these inventors, Robl, Collas, Sullivan, and Kasinathan, contributed to the permeabilized cell technology utilized and covered by a subset of the Robl claims.[1] The other four inventors contributed to the additional subject matter claimed in the published Robl application. Thus, the Robl application in no way calls into question the inventorship of the present case.

Similarly Collas et al. (2002/0142397), as indicated above, claims methods directed to the use of reprogramming for the entirely different purpose of altering the fate of a somatic cell. The Collas techniques involve steps for changing the phenotype and characteristics of a somatic cell such that it exhibits the phenotype and characteristics of a different somatic cell. As is clear, this technique of producing one somatic cell from a different somatic cell differs substantially from the presently claimed technique of producing a cloned animal from a somatic cell. The correct inventors of the Collas application are Collas and Robl; the correct inventors of the present application are Robl, Collas, Sullivan, and Kasinathan.

[1] Certain of these individuals also contributed to other claimed subject matter in the Robl application.

The § 102(f) rejection should be withdrawn.

Rejection Based on Double Patenting

Claims 1-15 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending applications, Robl (2004/0068760) and Collas (2002/0142397). Applicants request that this rejection be held in abeyance as neither the claims in the cited applications nor the present application have been indicated to be allowable.

Information Disclosure Statements

Applicants draw the Examiner's attention to two Information Disclosure Statements filed in connection with this case: the first mailed August 13, 2004 and the second submitted herewith. Applicants request that the references listed on these two Statements be reviewed by the Examiner and initialed Forms PTO-1449 returned with the next Action from the Office.

Conclusion

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested.

If the Office believes that issues remain in this case, Applicants request that the Examiner contact the undersigned attorney to arrange an Examiner interview.

Enclosed is a Petition to extend the period for replying to the Office action for two months, to and including October 18, 2004 and a check for the extension fee of $215.00. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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